Lung Cancer Canada
133 Richmond St. W., Suite 208
Toronto, ON, M5H 2L3

February 6th, 2025

Subject: Application for Lung Ambition Award – Lung Cancer Canada

Dear Selection Committee,

I am submitting my application for the Lung Ambition Award, supported by Lung Cancer Canada, to advance my ongoing research in non-invasive tumor genotyping for early-stage non-small cell lung cancer (NSCLC). As an independent researcher at the CHUM Research Center (CRCHUM) and Assistant Professor in hematology-oncology at University of Montreal, my work focuses on developing investigator-initiated trials (IITs) and advancing precision oncology through next-generation sequencing (NGS)-based approaches. My long-term objective is to enhance diagnostic and therapeutic strategies for patients with NSCLC tumors through liquid biopsy evaluating circulating tumor DNA (ctDNA), including NSCLC screening and minimal residual disease (MRD) detection.

During my oncology residency and MSc degree under Dr. Bertrand Routy, MD, PhD, I contributed to studies on real-world outcomes and immune checkpoint inhibitor (ICI) response in advanced NSCLC (EJC 2021, Cancer Discov. 2021, Nat Med 2022). I also initiated academic IITs evaluating molecular biomarkers of response to ICI in NSCLC such as CRYOVATE (NCT04793815) (JTO CRR 2024). Building on this experience, I completed a research fellowship at Memorial Sloan Kettering Cancer Center (MSKCC) in New York. My research there focused on NGS-driven clinical trials in NSCLC, genomic biomarkers of resistance, and emerging targeted therapies.

Since the start of my career, I have contributed to 30 indexed publications, completed seven IITs, and received awards such as the ASCO Conquer Cancer Merit Award. At CRCHUM, I lead initiatives to expand clinical NGS capacity through collaborations with the Therapeutic Innovations Unit (UIT) and as the Co-Director of the Guy Lafleur Precision Oncology Program at CRCHUM. Aligned with these efforts, my research proposal, "Non-invasive tumor genotyping in early-stage NSCLC using whole-genome, ultradeep sequencing with duplex adapters," aims to overcome limitations of invasive diagnostics in early-stage NSCLC. This project leverages high-sensitivity ctDNA assays to enable accurate tumor-uninformed genotyping and earlier diagnosis of NSCLC to improve patient outcomes.

The study's core objectives are:

Aim 1: Validate the performance of an ultradeep WGS-based ctDNA assay with duplex adapters in 30 patients by comparing ctDNA results with tissue-based WGS.
Aim 2: Develop a framework to integrate ctDNA genotyping into CHUM's lung cancer screening program, enhancing early detection while reducing reliance on invasive procedures.

Through recent work at Cornell University by collaborator Dr. Alexandre Pellan-Cheng, preliminary data show that our ultradeep WGS-based ctDNA with duplex adapters can detect MRD with a sensitivity threshold of 10^{-5} tumor fraction. By improving diagnostic workflows, this approach seeks to facilitate early detection, optimize patient care, and reduce healthcare burdens.

I believe this research aligns with the mission of the Lung Ambition Award to advance innovative lung cancer solutions. Thank you for your consideration of my application. I look forward to the opportunity to contribute to this important initiative.

Sincerely,

Antoine Desilets, MD, MSc
Hematologist-Oncologist, Department of Medicine, CHUM
Regular Researcher, Cancer Axis, CRCHUM
Co-Director, Guy-Lafleur Precision Oncology Program, CRCHUM
Assistant Professor, University of Montreal

Non-invasive tumor genotyping in early-stage non-small cell lung cancer (NSCLC) using whole-genome, ultradeep sequencing with duplex adapters

Background and rationale: Non-small cell lung cancer (NSCLC) remains the leading cause of cancer mortality in Canada[1], with recurrence rates in resectable NSCLC reaching up to 40% in stage IA (AJCC7) NSCLC[2,3]. Early-stage NSCLC presents significant diagnostic and therapeutic challenges due to reliance on invasive diagnostic procedures, such as endobronchial ultrasound (EBUS) and bronchoscopy-guided biopsies. These procedures are associated with complications, delays, and limited tissue yield, often impeding timely genotyping. Recent developments in liquid biopsy technology, particularly circulating tumor DNA (ctDNA) assays, offer a non-invasive alternative to traditional diagnostics by detecting tumor-derived genomic alterations in plasma, with improved prognostic value when compared to standard imaging or PD-L1 status[4,5]. However, most ctDNA assays are tumor-informed, requiring prior tumor biopsy and sequencing, which restricts their utility in cases of insufficient or inaccessible tumor tissue[6].

To overcome these limitations, this project proposes using ultradeep WGS with duplex adapters for tumor-uninformed ctDNA assays. This approach can provide sensitive and accurate genotyping without the need for prior tumor sequencing, building on advancements by bioinformatic engineer and CRCHUM collaborator Dr. Alexandre Pellan Cheng, PhD[7], who trained at Cornell University and worked with me in New York during my research fellowship at Memorial Sloan Kettering Cancer Center. This proposal also leverages the thoracic oncology infrastructure at CHUM, the highest-volume center for early-stage NSCLC in Quebec. Although previously limited by financial constraints, WGS costs are projected to exponentially decline in the coming years, driven by initiatives like Ultima, which are developing technologies soon capable of delivering a $100 genome[7,8].

Hypothesis: Whole-genome, ultradeep sequencing of ctDNA with duplex adapters can deliver accurate tumor-uninformed genotyping in early-stage NSCLC. This method can enable non-invasive confirmation of NSCLC diagnosis while also facilitating timely molecular characterization for personalized treatment approaches. The strategy aims to reduce the need for invasive procedures and enhance early detection and diagnostic efficiency.

Aim 1: Validate the performance of a tumor-uninformed ctDNA assay for genomic profiling in a priori biopsy-confirmed early-stage NSCLC patients (n = 30).

- *Objective*: Assess the sensitivity, specificity, and concordance of ctDNA-based genotyping compared to tissue-based WGS (already funded).
- *Methods*: Plasma samples will be collected from patients with biopsy-confirmed NSCLC *before* undergoing neoadjuvant treatment or surgery. This includes 20 retrospectively identified patients with stage IB-IIIA NSCLC already included in the CRCHUM lung biobank, led by collaborator Dr. Bertrand Routy, MD, PhD. Additional enrollment of n=10 patients with stage IA NSCLC will occur through an investigator-initiated trial (IIT) opening at CHUM in 2025 under my leadership (NCT06743581), funded by a New York CRI grant with CTA NOL already obtained from Health Canada (see Appendix). Following ctDNA extraction and processing by my team, WGS with duplex adapters will be performed at the CRCHUM, in collaboration with Dr. Pellan Cheng's bioinformatic pipeline.
- *Outcome*: Sensitivity, specificity, and concordance rates with tissue-based sequencing will be evaluated. Detection rates of clinically actionable mutations (e.g., *KRAS, BRAF*) will demonstrate the clinical utility of the tumor-uninformed approach.

Aim 2: Develop a framework for integrating tumor-uninformed ctDNA assays into the CHUM lung cancer screening program and lung nodule diagnostic pathways (n=10).

- *Objective*: Explore the feasibility of incorporating ctDNA genotyping into screening programs to reduce reliance on invasive diagnostic procedures.
- *Methods*: Data from Aim 1 will inform a pilot study at CHUM's lung cancer screening program, targeting high-risk patients eligible for low-dose CT (LDCT) screening. Plasma samples from these patients will undergo ctDNA WGS using duplex adapters.
- *Outcome measures*: Early detection rates of NSCLC through ctDNA and concordance with LDCT findings will be assessed. Improvements in patient care pathways will also be analyzed.

Significance: This study aims to validate a tumor-uninformed ctDNA assay for non-invasive genomic profiling in early-stage NSCLC. By addressing the limitations of both tissue-based diagnostics and tumor-informed liquid biopsies, this research seeks to improve diagnostic workflows, reduce healthcare burden, and enhance early-stage lung cancer management. Successful implementation could lead to the provincial integration of ctDNA screening into existing cancer detection programs.

Preliminary data: Preliminary results from collaborator Dr. Pellan Cheng indicate that WGS with duplex adapters reduces error rates to approximately 10^{-7}, significantly enhancing sensitivity to detect tumor fractions as low as 10^{-5}. This high-fidelity sequencing enables robust ctDNA detection even in minimal residual disease (MRD) contexts such as stage I NSCLC, overcoming limitations posed by tumor tissue and laying the foundation for early NSCLC detection strategies[7].

Methodology:
- *Patient population*: Early-stage NSCLC patients undergoing diagnostic biopsy, neoadjuvant chemo-immunotherapy at CHUM (resectable stage IB-IIIA), and those enrolled in CRCHUM lung biobanking. This includes patients from the NCT06743581 IIT for which I act as PI (total enrolment of n = 24 patients with stage IA NSCLC, with 12 patients enrolled per year).
- *Sample collection*: Plasma will be collected at baseline (before surgery or initiation of neoadjuvant chemo-IO) for non-invasive WGS-based tumor genotyping with duplex adapters.
- *Sequencing*: ctDNA extraction and pre-analytics will be performed at CRCHUM by my team. WGS with duplex adapters will be conducted at CRCHUM, powered by the Guy Lafleur Precision Oncology Program.
- *Data analysis*: Mutational profiles will be generated using bioinformatic pipelines optimized for high-depth sequencing and low-input ctDNA samples. Concordance with tissue-based sequencing will be evaluated using Fisher's exact test and logistic regression.

Anticipated outcomes:
1. High concordance between tumor-uninformed ctDNA and tissue-based genomic profiling, paving the way for non-invasive tumor genotyping approaches.
2. Enhanced early detection and prognostic capabilities through non-invasive methods.
3. Development of a scalable ctDNA-based screening framework to complement LDCT programs, reducing radiation exposure, diagnostic delays, and healthcare burden.

IMPACT STATEMENT

This project aims to reduce lung cancer mortality and improve patient quality of life by advancing non-invasive genomic profiling. The proposed tumor-uninformed ctDNA genotyping strategy, if validated, will transform early-stage NSCLC diagnosis by reducing reliance on invasive procedures and enabling broader, timely access to genomic data for personalized treatment. Integration into screening programs for high-risk populations will enhance early detection, reduce diagnostic delays, and lower healthcare costs. By improving sensitivity through whole-genome sequencing with duplex adapters, this approach addresses limitations of current biopsy and liquid biopsy methods. These advancements will optimize clinical workflows, improve survival outcomes, and reduce the burden of lung cancer within the healthcare system.

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PUBLIC, NON-SCIENTIFIC SUMMARY

Lung cancer is the leading cause of cancer-related deaths in Canada. Even when diagnosed early, non-small cell lung cancer (NSCLC) often returns after treatment in up to 40% of cases. Diagnosing and analyzing early-stage NSCLC can be challenging because it typically requires invasive procedures like biopsies, which can cause complications and may not always provide enough tissue for testing. These delays can hinder timely and accurate treatment decisions. However, a new approach known as liquid biopsy offers an alternative approach. By analyzing small fragments of tumor DNA found in a patient's blood (circulating tumor DNA or ctDNA), doctors can detect cancer and learn about its characteristics without the need for surgery or invasive tests. Despite its promise, most ctDNA tests still rely on having a sample of the tumor for comparison, which limits their usefulness when obtaining a tumor sample is difficult.

This project aims to develop a new, non-invasive method to detect and analyze NSCLC using advanced whole-genome sequencing (WGS) with "duplex adapters." This technology allows for extremely precise DNA analysis without needing a tumor biopsy. The first goal is to test the accuracy of this approach by comparing blood-based genetic analysis with traditional tissue-based results from patients already diagnosed with early-stage NSCLC. We will also assess how well this new test can detect key mutations that could guide treatment. The second goal is to explore how this technique might be integrated into screening programs for people at high risk of developing lung cancer. We hope this method will improve early detection and reduce the need for invasive tests like biopsies.

If successful, this approach could revolutionize how lung cancer is diagnosed and treated, making the process faster, safer, and more accessible for patients. By enabling earlier detection and personalized treatment, we aim to improve outcomes, reduce healthcare costs, and ultimately save lives.

BUDGET

Personnel:

- Imen Ben Aissa, MSc (research assistant and data analyst with laboratory experience human genetics, bioinformatics and databank management; salary already covered by Antoine Desilets' CRCHUM start-up funds).
- Wiam Belkaid, PhD (research associate and regulatory expert with significant expertise in clinical trial management, Health Canada and Clinical Trial Applications, contract negotiation and study monitoring; salary already covered by CRCHUM start-up funds).
- Anna Perez, BSc (research coordinator with experience as a clinical study lead coordinator at McGill University including informed consent forms, case report files, study monitoring and adverse event reporting; salary already funded by a Cancer Research Institute grant).
- Julie Malo, RN (lung biobank coordinator; salary covered by the Cancer Axis at CRCHUM).

Collaborators:

- Alexandre Pellan Cheng, PhD (bioinformatician and collaborator, salary not covered by this grant).
- Bertrand Routy, MD, PhD (hematologist-oncologist and researcher, director of CRCHUM lung biobank, salary not covered by this grant, co-PI for the NCT06743581 clinical trial).

Consumables: ctDNA extraction kits, library preparation reagents = $50 per patient. The cost per ctDNA assay is $1,050. Total cost per sample is 1,150$. Liquid biopsy validation will include n=40 patients: n=20 with stage IB-IIIA from the CRCHUM lung biobank, n=10 patients with stage IA NSCLC from the NCT06743581 trial, and n=10 patients with lung nodules detected as part of CHUM screening program. Please refer to Budget table below. The NCT06743581 clinical trial is supported by my CRI grant, except for proposed liquid biopsy correlative analyses which are not currently covered.

Equipment: Library preparation and sequencing will be conducted at the CRCHUM, which is equipped with Illumina NovaSeq X sequencers through the Guy-Lafleur Oncology Program and recent transformative Durocher philanthropic funds, offering high-throughput WGS capacity. Samples will be analysed in two batches: the first batch after Q1-Q3 of 2025 including n=30 patients from the CHUM lung biobank or the NCT06743581 trial, and a second batch with n=10 patients from the CHUM lung cancer screening program.

Quarter	Task	Cost (CAD)	Percentage
Q1-Q2 2025	1. Clinical trial enrolment of first 10 patients with stage IA NSCLC in NCT06743581	0	0%
	2. Prior enrolment of n=20 retrospectively biobanked patients with stage IB-IIIA NSCLC in CRCHUM lung biobank	0	0%
	3. First batch of n=30 samples from patients with biopsy-confirmed early-stage NSCLC analysed using whole-genome, ultradeep sequencing with duplex adapters	36 000	72%
Q3-Q4 2025	1. Complete enrolment of n=10 patients from the CHUM lung cancer screening program	0	0%
	2. Second batch of n=10 samples without a priori biopsy-confirmed NSCLC sent for whole-genome, ultradeep sequencing with duplex adapters at CRCHUM	12 000	24%
	3. Knowledge dissemination at national conference	2 000	4%
Total	Total budget	50 000	100%

CRCHUM
CENTRE DE RECHERCHE
Centre hospitalier
de l'Université de Montréal

Université de Montréal

Montreal, February 5th 2025

Dr. Antoine Desilets (MD, MSc)
Centre de recherche du CHUM (CRCHUM)

OBJECT: Letter of institutional support for Dr. Desilets, MD, MSc – Lung Cancer Canada – Lung Ambition Award

Dear Committee Members,

I hereby wish to express my strong support for Dr. Antoine Desilets' application for the Lung Ambition Award competition. Dr. Desilets' research program, which focuses on enhancing personalized medicine for early-stage non-small cell lung cancer patients through whole genome sequencing, aligns perfectly with the Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM) commitment to advancing innovative cancer treatments through clinical and translational research.

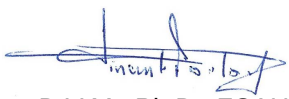
Dr Desilets joined the CRCHUM at the beginning of January 2025. He is a highly accomplished and driven early-career researcher in hemato-oncology, with regular researcher status within the CRCHUM Cancer Axis and an Assistant Professor of Medicine at the Université de Montréal. Being part of the Cancer research theme provides numerous collaboration opportunities and expertise-sharing among highly experienced researchers. Recently, Dr. Desilets was appointed Co-Director of the Guy-Lafleur Precision Oncology Program at CRCHUM, working alongside Dr. Anne-Marie Mes-Masson, Scientific Director at CRCHUM.

I confirm that the proposed research is feasible within our institution and that Dr. Desilets's team will have access to state-of-the-art facilities essential for the project, including high-capacity sequencers for whole genome sequencing, common specialized equipment and the CRCHUM core facilities, along with technical support. Dr Desilets' full research status at our institution ensures a minimum of 50% of protected time for research and remuneration for research time, access to a computer, storage space on the CRCHUM servers, benefit from identified spaces within our institution, usage of shared instruments and services of 19 available platforms for which the services are subsidized up to 40%.

Our institution acknowledges and accepts the grant application guidelines and is fully committed to supporting Dr Desilets throughout the award period. We will provide ongoing administrative assistance and will ensure the management of financial reporting. We are particularly excited about the potential impact this research program could have on the outcomes of patients with early-stage non-small cell lung cancer.

Please accept, dear members of the committee, my warmest regards.

Director of Research and Innovation - CHUM and Scientific Director - CRCHUM,



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